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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,606	04/11/2005	Michael Vajdy	PP18892.003	9598

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EXAMINER	
SNYDER, STUART	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,606	VAJDY ET AL.	
	Examiner	Art Unit	
	Stuart W. Snyder	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *3, 17-31 and 37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-16 and 32-36* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/2007 has been entered.

Claims 1-40 are pending; claims 1, 2,4-16 and 32-36 are subject to examination and the remaining claims were withdrawn as pertaining to unelected subject matter.

Claim Objections

2. Claim 34 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 33. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case Claim 33 depends on Claim 32, which, in turn, depends on Claim 1. Claim 33 ultimately limits the amount of env-derived antigen of the composition of Claim 1 to "about 100 μg". Claim 34 directly depends on Claim 1 and limits the amount of env-derived antigen of the composition Claim 1 to "about 100 μg". Thus each limits the amount of limits the amount of env-derived antigen

of the composition to "about 100 μg" and therefore Claim 34 is essentially a duplicate of Claim 33.

3, Objection to Claim 36 as allowable but dependent on claim 5 is withdrawn.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 2, 4-10, and 13-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vajdy, et al. in view of Keefer, *et al.* The claims are drawn to a composition comprising HIV envelope antigen (env) and, as elected, LTK63 wherein env is in an amount of about 0.1 to about 1000 μg (claims 1 and 2). Additional dependent claims add the limitation that LTK63 is required to be a holotoxin (claim 4); env selected from gp120, gp160 and Ogp140 (claim 5); env is optimized for immunogenicity (claim 6); the composition of claim 1 further comprises an additional HIV antigen (claim 7) that is optimized for immunogenicity (claim 8) and selected from HIV structural, regulatory or accessory proteins (claim 9); wherein the structural protein is selected from gag-, pol-, and env-encoded proteins (claims 10 and 14 (gag)); and the composition is suitable for intranasal, intravaginal or intrarectal delivery.

Vajdy, et al. teaches intranasal administration of Ogp140, gag (p55) or p55-VLP each with or without the holotoxin LTK63; Vajdy, et al. indisputably teaches all of the limitations of claims 1-2 and 4-6 with the exception of the claimed range of the env antigen and which is traversed by Applicant.

Applicant argues that "Vajdy's Abstract does not disclose any amounts whatsoever of HIV Env antigen and does not teach that the presence of LTK63 enhances the immune response generated against HIV Env antigens". Concerning the first aspect of the statement and arguments: Vajdy, et al. does, in fact, teach an amount of env in the composition, to wit, an amount > 0 μg—this fact is implicit in the statement that the mice were immunized with Ogp140. Concerning the second aspect of the statement regarding increased immunogenicity of co-administration of env and LTK63 relative to administration of env alone: None of the claims require such a limitation and thus the argument is moot regarding the applicability of the art for an obviousness rejection. Returning again to the applicability of Vajdy, et al. regarding whether a specific range of the mass of env confers patentability, the excerpts of the CAFC are quite clear and unambiguous:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955)" and
>
> "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re: Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)".

As applied to Vajdy, et al., In re: Aller suggests that claim 1 recitation of a specific range is not inventive, i.e., obvious over Vajdy, et al. because the cited range is clearly within the range >0 mg. In re: Antonie requires that a parameter, in the instant case the mass of env antigen in the composition, be recognized as a result-effective variable. Keefer, et al. establishes that increased mass of env administered to mice results in an increased env-specific immune response. There is no teaching in Vajdy, et al., Keefer, et al., other art of record, or the specification that co-administration of LTK63 interferes with this result-dependent variable. Thus, Applicants' arguments concerning the non-obviousness of the particular range are not found to be persuasive.

Applicant further states that Vajdy, et al. "is entirely focused on dual administration of env- and gag-derived antigens". The Examiner finds this statement confusing; does Applicant assert that Vajdy, et al. teaches co-administration of the two HIV-derived antigens? If so, this is not readily apparent in the simplest interpretation of the abstract. If Applicant is asserting that the point of the abstract is to teach env-derived antigens co-administered with LTK63 and gag-derived antigens co-administered with LTK63 induce a broader immune response (both humoral and cell-mediated), the Examiner has no dispute. The Examiner further agrees with Applicants' assertion that "the abstract teaches away from administration of env alone"; the abstract clearly teaches administration of either env- or gag-derived antigens to achieve humoral and/or cell-mediated immune responses to the HIV-derived antigens.

Applicant further argues that inclusion of LTK63 in immunogenic compositions is critical to producing an immune response. However, others have achieved 100% responses to gp120-based vaccines (see, Kumar, et al. page 2) in both arms of vaccinees immune responses; high titers of anti-gp120 antibodies and transient CTL responses following immunization. The Examiner agrees that inclusion of LTK63 seems to enhance the immunogenicity of subunit-based env- or gag-derived vaccines; however the question of criticality must be viewed in the context of efficacy when challenged with the pathogen because it is clear that immune responses to HIV-derived antigens is insufficient to protect vaccinees from infection although such responses may be important to delay the course of the disease (see Kumar and Narayan especially page 2 starting with the first complete paragraph beginning with the words "Although the gp120 vaccine failed to elicit...").

Concerning rejected claims 7-10 and 13-16: Vajdy, et al. does not specifically teach a composition comprising env- and gag-derived antigens in combination with LTK63. However, the goal of Vajdy, et al. as well as the instant application is clearly to develop an HIV vaccine useful for prevention or treatment:

"...a vaccine that can protect the mucosa at the site of [HIV] entry is much warranted" (Vajdy, et al., second sentence), and

"Preferably, the pharmaceutical compositions of the invention can be used to treat or prevent HIV infection" (Second sentence of the instant invention as originally filed).

It would have been obvious to one of skill in the art at the time of filing to combine the two HIV-derived antigens together with LTK63. One of skill in the art would have been motivated to make the claimed compositions because it was thought at the time that inclusion of other structural, accessory and/or regulatory proteins would lead to a more complete immune response and thus a more effective anti-HIV vaccine than either alone in combination with LTK63. One of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed compositions for the intended use of treating or preventing HIV because recombinant gp120-based subunit vaccines have been shown to induce anti-HIV neutralizing antibodies as well as anti-HIV CD4 T cell proliferative responses whereas gag-based subunit and VLP vaccines have been shown to induce anti-HIV CD4 T cell proliferative responses, CD8 CTL responses as well as anti-HIV neutralizing antibodies (see Haynes, et al. Table on page 934).

Further, the courts have said: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose . . . ". [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). In this case, applicants are combining two known HIV immunogens with LTK63.

Finally, Applicants argue that the Examiner previously asserted that Applicants are entitled to claim only that which is exemplified. The Examiner regrets that Applicants misconstrued the previous Office action. The Examiner clearly understands that Applicants may claim all aspects of the invention that are enabled by the specification. However, it was the point of paragraph 2 of the latest Final Rejection to assert that the claimed range was obvious over the cited combined references for the reasons more fully explained above.

Therefore, the invention of claims 1, 2, 4-10, and 13-16 is prima facie obvious to one of ordinary skill in the art at the time the invention was made and the rejection of the claims under 35 USC 103(a) is maintained.

4. Claims 1, 11 and 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vajdy, et al. in view of Keefer, et al. as applied to claims 1, 2, 4-10 and 13-16 above and in further view of Kumar and Narayan, Haynes, et al., Kang, et al, Tobery and Siliciano, Cease and Berzofsky and Vogel. The claims are drawn to compositions of env-derived antigens and LTK63 in combination with regulatory proteins (claim 10) or accessory proteins (claim 11) of HIV. Applicants rebut the rejection because the Examiner used the motivation "broadest the scope of the immune response" in the Final Rejection of 12/19/2006. Applicants argue that a skilled artisan would not have been motivated by such a reason nor is the motivation taught by the any of the cited references.

Applicants' arguments have been carefully studied and are not found to be persuasive for reasons of record and the following: Haynes clearly teaches increasing the breadth of HIV immune response to encompass more that antibody and CTL responses to env-based subunit vaccines. The entire section entitled "What are HLA-based HIV vaccines?" concerns induction of T-cell immunity via multivalent mixtures of immunogens and "containing sufficient immunogenic CTL and T helper epitopes capable of binding to the HLA molecules expressed on antigen-presenting cells..." (Haynes, p 935). In the next column, Haynes explicitly recites immunogenic and anti-HIV CTL inducing epitopes from gag, nef, gp41, and gp120 based on HLA allotypes of the target population. Haynes further teaches use of cholera toxin or other antigens useful for inducing genital and gastrointestinal mucosal T and B cell immunity to HIV (p 936, column 1, "What do we need to accomplish in future studies?" referring to Staats, et al.); Staats, et al., in turn, explicitly teaches the use of holotoxins derived from E. coli enterotoxins in combination with subunit based vaccines for mucosal vaccination (see Staats, et al., page 468, column 1). Thus, in contrast to Applicants arguments concerning use of LTK63 in combination with various HIV-derived subunit immunogen, there was motivation by those skilled in the art to include bacterial toxins in combination with env-based and other HIV-derived immunogens at the time of filing of the instant Application.

Rejection of claims 1, 11 and 12 under 35 U.S.C. 103(a) over Vajdy, et al. in view of Keefer, et al. in further view of Kumar and Narayan, Haynes, et al., Kang, et al, Tobery and Siliciano, Cease and Berzofsky and Vogel is proper and **maintained**.

5. Claims 32-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vajdy, et al. in view of Keefer, et al. as applied to claims 1, 2, 4-10 and 13-16 above and in further view of Kumar and Narayan. The claims are drawn to compositions of LTK63 in combinations with specific ranges or amounts of HIV env-derived antigens.

Applicants argue that the claimed ranges and/or amounts of env-derived antigens are not obvious from the cited art because:

Vajdy, et al. does not teach a particular amount of HIV env-derived antigen,

Keefer, et al. does not teach ogp140 or LTK63 and allegedly teaches away from using less than 640 μg of env-derived antigen—Applicants at this point suggest that no motivation exists on this basis alone, and

since there is no combined teaching between Vajdy, et al. and Keefer, et al. to arrive at the composition of Claim 1 and no motivation even to combine these teachings there can be no rescue of the alleged deficiencies by adding Kumar and Narayan to narrow the range of env-derived antigen.

The Examiner has carefully studied Applicants' arguments and has not found them persuasive for reasons of record, those presented above relevant to the range presented in claim 1, and the following:

The Examiner maintains the position that use of ogp140 or other env-derived subunit immunogens taught by Vajdy, et al. in intranasal inoculation of mice renders obvious determining an optimal amount of immunogen,

Keefer, et al. was a report of an extension of clinical trials in HIV-negative humans to determine the safety and immune response to a recombinant, baculovirus env-based subunit vaccine adjuvanted with aluminum phosphate gel and administered on at least 4 occasions over a one year and followed for an additional year; the full range of the study was 40-640 μg,

in their discussion, Keefer, et al. cites similar studies wherein the amount of recombinant env-based antigen administered per inoculation was in the range of 10-1280 μg, 12.5 or 50 mg, or 100-600 mg,

Keefer, et al. further discuss results of one of the studies (Kovacs, et al) that used a similar antigen but with a different adjuvant (AlOH plus deoxycholate) that achieved results similar to the Keefer, et al. but at approximately 10-fold lower concentrations, and

It was well known at the time of filing to those of ordinary skill in the art of vaccinology that different adjuvants enhance antigens differently and that some do not provide the desired additional immunostimulatory effect with all antigens (see Kenney and Edelman, p 172, Limited adjuvanticity).

In sum, the range of env-derived antigen in Claim 1 encompasses or overlaps with ranges well known in the art whereas those of claims 32-35 are basically

optimized or preferred dosages that are obvious to those skilled in the art and determinable by well-established dose-response protocols. The dose-response protocols are standard, obvious clinical trials necessary for any novel vaccine or reformulated vaccine for human or animal use where regulation by international, national or local regulatory agencies is appropriate. Therefore, the invention of claims 32-35 is obvious in view of the cited literature and the rejection is **maintained.**

6. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vajdy, et al. in view of Keefer, *et al.* The claim is drawn to a composition comprising the HIV envelope-derived antigen (Ogp140) and, as elected, LTK63 wherein Ogp140 is in an amount of about 0.1 to about 1000 μg (claims 1 and 36). The Examiner previously indicated that claim 36 contained allowable subject matter, however upon careful reconsideration the Examiner holds that it also is unpatentable for the following reasons.

The specification teaches that Ogp140 consists of deletion and modification of gp160; i.e., the polyprotein encoded by the env gene is truncated to remove the membrane anchoring region normally found in the mature protein gp41, the normal protease cleavage site is modified as stated in claim 36 so that the site is not recognized by the cellular protease, and the codon usage is optimized for efficient production.

Vajdy, et al. teaches intranasal administration of Ogp140 with or without the holotoxin LTK63. Thus, Vajdy, et al. indisputably teaches all of the limitations of

claims 1 and 36 with the exception of the claimed range of the Ogp140 antigen and which Applicant traverses.

Applicant argues that "Vajdy's Abstract does not disclose any amounts whatsoever of HIV Env antigen and does not teach that the presence of LTK63 enhances the immune response generated against HIV Env antigens".

Concerning the first aspect of the statement and arguments: Vajdy, et al. does, in fact, teach an amount of Ogp140 in the composition, to wit, an amount > 0 μg—this fact is implicit in the statement that the mice were immunized with Ogp140.

Concerning the second aspect of the statement regarding increased immunogenicity of co-administration of env and LTK63 relative to administration of env alone: None of the claims require such a limitation and thus the argument is moot regarding the applicability of the art for an obviousness rejection.

Returning again to the applicability of Vajdy, et al. regarding whether a specific range of the mass of Ogp140 confers patentability, the excerpts of the CAFC are quite clear and unambiguous:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955)" and
>
> "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as

routine experimentation. In re: Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)".

As applied to Vajdy, et al., In re: Aller suggests that claim 1 recitation of a specific range is not inventive, i.e., obvious over Vajdy, et al. because the cited range is clearly within the range >0 μg. In re: Antonie requires that a parameter, in the instant case the mass of Ogp140 in the composition, be recognized as a result-effective variable. Keefer, et al. establishes that increased mass of env administered to mice results in an increased env-specific immune response. There is no teaching in Vajdy, et al., Keefer, et al., other art of record, or the specification that co-administration of LTK63 interferes with this result-dependent variable. Thus, Applicants' arguments concerning the non-obviousness of the particular range are not found to be persuasive.

Conclusion

7. No claims are allowed.

8. Applicant is encouraged to provide, for the record, slides or the poster presented by one of the Inventors at the 2000 CROI as definitive rebuttal of Examiner's 103(a) rejection concerning the criticality the ranges and amounts of env-derived antigens recited in claims 1 and 32-36 as well as the criticality of LTK63 to elicit a more robust immune response to subunit-based vaccines relative to compositions comprising the subunit antigens without LTK63.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart W. Snyder whose telephone number is (571) 272-9945. The examiner can normally be reached on 9:00 AM-5: 30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stuart W Snyder
Examiner
Art Unit 1648

SWS

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER